Part I Overview Information

Department of Health and Human Services

Participating Organizations
National Institutes of Health (NIH), (http://www.nih.gov/)
Tuberous Sclerosis Alliance (TS Alliance), (http://www.tsalliance.org)

Components of Participating Organizations
National Institute of Neurological Disorders and Stroke (NINDS), (http://www.ninds.nih.gov)
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), (http://www.niddk.nih.gov/)
National Institute of Mental Health (NIMH), (http://www.nimh.nih.gov)
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), (http://www.niams.nih.gov)
National Cancer Institute (NCI), (http://www.nci.nih.gov)

Title: Understanding and Treating Tuberous Sclerosis Complex

Announcement Type
This is a new Program Announcement with set-aside funds (PAS)

Program Announcement (PA) Number: **PAS-05-085**

Catalog of Federal Domestic Assistance Number(s)
93.853, 93.849, 93.242, 93.846, 93.396

Key Dates
Release Date: April 11, 2005
Letters of Intent Receipt Date(s): Not Applicable
Application Receipt Dates(s): Standard dates apply, please see http://grants.nih.gov/grants/funding/submissionschedule.htm for details
Peer Review Date(s): Standard dates apply, please see http://grants.nih.gov/grants/funding/submissionschedule.htm for details
Council Review Date(s): Standard dates apply, please see http://grants.nih.gov/grants/funding/submissionschedule.htm for details
Earliest Anticipated Start Date: April 2006
Additional Information To Be Available Date (Url Activation Date): Not Applicable
Expiration Date: March 2, 2008

Due Dates for E.O. 12372
Not Applicable

Additional Overview Content

Executive Summary

- The National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Mental Health (NIMH), National Cancer Institute (NCI), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the Tuberous Sclerosis Alliance invite research grant applications aimed at understanding or treating Tuberous Sclerosis Complex (TSC).
- The participating organizations intend to commit a total of approximately $2,000,000 to this PAS in addition to funds available for applications sent in response to this initiative that score within the paylines of the participating NIH Institutes..
- Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary. The total amount awarded and the number of awards will depend upon the mechanism numbers, quality, duration, and costs of the applications received.
- This PAS will use the NIH R01, R21 and R03 mechanisms.
- Eligible organizations include: for-profit or non-profit organizations; public or private institutions, such as universities, colleges, hospitals, and laboratories; units of State and local governments; eligible agencies of the Federal government; and domestic or foreign institutions/organizations ; faith-based or community-based organizations.

- Eligible principal investigators include any individual with the skills, knowledge, and resources necessary to carry out the proposed research. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.
- There is no limit to the number of scientifically different applications each applicant may submit.
- The PHS 398 application materials are available at http://grants.nih.gov/grants/funding/phs398/phs398.html.
- Telecommunications for the hearing impaired is available at: TTY 301-451-0088.

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Part II - Full Text of Announcement

Section I. Funding Opportunity Description

1. Research Objectives

Purpose of this PA

The National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Mental Health (NIMH), National Cancer Institute (NCI), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the Tuberous Sclerosis Alliance invite research grant applications aimed at understanding or treating Tuberous

Sclerosis Complex (TSC). The genes that cause TSC (TSC1 and TSC2) are known, understanding of the pathways in which they act is increasing, and animal models that mimic certain features of the disease now exist. As a result, there is a remarkable opportunity to increase our knowledge about the mechanisms that cause TSC and translate this knowledge into therapies for this often devastating disorder. Included within the scope of this PA are molecular genetic, developmental, and pathophysiological studies, preclinical therapy development and clinical research.

Background

TSC is a multi-system disease that causes benign tumors (hamartomas) to form at multiple sites throughout the body. Hamartomas can develop in many different organs, primarily the brain, lungs, heart, kidney, skin, and eyes. In most affected individuals, only a subset of these organs is affected. Epileptic seizures (which often begin as infantile spasms) and learning and behavioral problems are also common. There is no cure for TSC; treatment is symptomatic and may include anticonvulsant therapy for seizures, drug therapy for neurobehavioral problems, treatment of high blood pressure caused by kidney dysfunction, and surgery to remove growing tumors. The prognosis for individuals afflicted with TSC varies in accordance with the severity of the specific symptoms. While severe manifestations may be seen in individuals diagnosed in childhood, mild forms of the disease may be observed in men and women diagnosed in adulthood.

TSC is a genetic disease, but more than half of affected individuals have spontaneous rather than inherited mutations. The disease is associated with mutations in either the TSC1 or TSC2 genes, which encode the proteins hamartin and tuberin. The two proteins bind to each other and are likely to act as tumor suppressors. Recent evidence shows that the TSC gene products normally act to inhibit the protein kinase mTOR in a conserved signaling pathway involved in nutrient uptake, cell growth and protein translation. A variety of mouse models of TSC are now available, providing an opportunity to understand disease mechanisms and evaluate candidate therapeutic agents.

Scope

Applications submitted in response to this PA should focus on a topic related to understanding or treating TSC. Studies with the potential to identify new therapeutic targets or that involve preclinical testing of candidate therapeutics are particularly encouraged. Possible topics include, but are not limited to:

- Studies of the role of hamartin and tuberin in basic cellular processes (e.g. nutrient sensing, signal transduction, and cell death) and development. Novel hypotheses are particularly encouraged.
- Development of more sophisticated animal models for TSC. Such models could permit the spatial or temporal regulation of TSC1 or TSC2 expression and/or permit the testing of candidate therapeutics. Models that mimic specific TSC symptoms are encouraged.
- Development of cell culture models of TSC. Models that permit high-throughput screening of small-molecule therapeutics are of particular interest.
- Identification of the downstream targets of tuberin and hamartin, with particular emphasis on potential molecular targets for drug therapy
- Developmental, neuroanatomical, electrophysiological, and imaging studies intended to identify specific abnormalities in TSC patients or in animal models of TSC
- Elucidation of the molecular events that cause lesions to develop in specific tissues (e.g. brain, lungs, heart, kidneys, and skin)
- Investigation of the pathogenesis of TSC-associated skin lesions and testing of potential therapeutic compounds to treat these lesions
- Studies aimed at understanding and developing treatments for TSC-associated infantile spasms and epilepsies
- Assessment and treatment of TSC-associated cognitive and behavioral problems, including both pharmacological and non-pharmacological interventions
- Investigation of the role of the TSC1 and TSC2 gene products in other disorders (e.g. PKD, Type 2 diabetes, renal cell carcinoma, lymphangioleiomyomatosis)
- Pre-clinical screening of potential small-molecule or gene-based therapies in cellular or animal models of TSC
- Neurodevelopmental and longitudinal studies of TSC patients that investigate the progression and inherent variability of the disease. Studies that will facilitate the future development of clinical trials are particularly encouraged.

See Section VIII, Other Information - Required Federal Citations, for policies related to this announcement.

Section II. Award Information

1. Mechanism(s) of Support

This funding opportunity will use the NIH Research Project Grant (R01), NIH Exploratory/Developmental Research Grant (R21; please see http://grants.nih.gov/grants/funding/r21.htm; and http://grants.nih.gov/grants/guide/pa-files/PA-03-107.html) and the NIH Small Grant Program (R03; please see http://grants.nih.gov/grants/funding/r03.htm; and http://grants.nih.gov/grants/guide/pa-files/PA-03-108.html) award mechanism(s). As an applicant, you will be solely responsible for planning, directing, and executing the proposed project.

The proposed project period during which the research will be conducted should adequately reflect the time required to accomplish the stated goals and should be no more than 5 years for R01 grants. Applicants are encouraged to contact program staff for advice about choosing the appropriate grant mechanism.

R21 grants are one-time awards intended to encourage new exploratory/developmental research projects by providing support for the early stages of their development. For example, such projects could assess the feasibility of a novel area of investigation or a new experimental system that has the potential to enhance health-related research. These studies may involve considerable risk but, if successful, will lead to a breakthrough in a particular area, or to the development of novel techniques, agents, methodologies, models or applications that could have major impact on a field of biomedical, behavioral, or clinical research.

The R03 award will support small research projects that can be carried out in a short period of time with limited resources. For example, the development of animal models may be particularly suited to the R03 mechanism. Examples of the types of projects that the participating ICs support with the R03 can be found at http://grants.nih.gov/grants/funding/r03.htm.
Competing continuation applications submitted in response to this PAS will compete with all investigator-initiated applications and be referred and reviewed according to the customary peer review procedures. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant.
This funding opportunity uses just-in-time concepts. It also uses the modular as well as the non-modular budget formats (see http://grants.nih.gov/grants/funding/modular/modular.htm). Specifically, if you are submitting an application with direct costs in each year of $250,000 or less, use the modular budget format described in the PHS 398 application instructions. Otherwise follow the instructions for non-modular research grant applications.

2. Funds Available

The participating organizations intend to commit a total of $2,000,000 to this Program Announcement with set-aside funds (PAS), in addition to funds available for applications sent in response to this PAS that score within the pay lines of the participating NIH Institutes. The total amount awarded and the number of awards will depend upon the mechanism, duration, and costs of the applications received, and are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications. R21 applications may request a project period of up to two years with a combined budget for direct costs of up to $275,000 for the two year period. For example, you may request $100,000 in the first year and $175,000 in the second year. The request should be tailored to the needs of your project. Normally, no more than $200,000 may be requested in any single year. For R03 applications, a project period of up to two years and a budget for direct costs of up to two $25,000 modules or $50,000 per year may be requested. Applications submitted in response to this program announcement will be accepted at the standard application deadlines (see: http://grants.nih.gov/grants/funding/submissionschedule.htm). The earliest possible start date for applications submitted in response to this program announcement is April 2006.
Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary. Although the financial plans of the IC(s) provide support for this program, awards pursuant to this funding opportunity are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications.
Facilities and administrative costs requested by consortium participants are not included in the direct cost limitation, see http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-004.html.

Section III. Eligibility Information

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1. Eligible Applicants

1.A. Eligible Institutions

You may submit (an) application(s) if your organization has any of the following characteristics:

- For-profit or non-profit organizations
- Public or private institutions, such as universities, colleges, hospitals, and laboratories
- Units of State and local governments
- Eligible agencies of the Federal government
- Domestic (or foreign) Institutions/organizations
- Faith-based or community-based organizations

1.B. Eligible Individuals

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

2. Cost Sharing or Matching

Cost Sharing is not required.
The most current Grants Policy Statement can be found at:
http://grants.nih.gov/grants/policy/nihgps_2003/nihgps_Part2.htm#matching_or_cost_sharing.

3. Other-Special Eligibility Criteria

There is no limit to the number of applications an applicant may submit under this announcement.

Section IV. Application and Submission Information

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1. Address to Request Application Information

The PHS 398 application instructions are available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. Applicants must use the currently approved version of the PHS 398. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.
Telecommunications for the hearing impaired: TTY 301-451-0088.

2. Content and Form of Application Submission

Applications must be prepared using the most current PHS 398 research grant application instructions and forms. Applications must have a D&B Data Universal Numbering System (DUNS) number as the universal identifier when applying for Federal grants or cooperative agreements. The D&B number can be obtained by calling (866) 705-5711 or through the web site at http://www.dnb.com/us/. The D&B number should be entered on line 11 of the face page of the PHS 398 form.

The title and number of this funding opportunity must be typed on line 2 of the face page of the application form and the YES box must be checked.

3. Submission Dates and Times

Applications must be mailed on or before the receipt date described below (Section IV.3.A). Submission times N/A.

3.A. Receipt, Review and Anticipated Start Dates

Letters of Intent Receipt Date(s): Not Applicable
Application Receipt Dates(s): Standard dates apply, please see http://grants.nih.gov/grants/funding/submissionschedule.htm for details
Peer Review Date(s): Standard dates apply, please see http://grants.nih.gov/grants/funding/submissionschedule.htm for details
Council Review Date(s): Standard dates apply, please see http://grants.nih.gov/grants/funding/submissionschedule.htm for details
Earliest Anticipated Start Date: April 2006

3.A.1. Letter of Intent

A letter of intent is not required for this funding opportunity.

3.B. Sending an Application to the NIH

Applications must be prepared using the PHS 398 research grant application instructions and forms as described above. Submit a signed, typewritten original of the application, including the checklist, and five signed photocopies in one package to:
Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710 (U.S. Postal Service Express or regular mail)
Bethesda, MD 20817 (for express/courier service; non-USPS service)

3.C. Application Processing

Applications must be **submitted on or before the application receipt dates** described above (Section IV.3.A.) and at http://grants.nih.gov/grants/dates.htm. Upon receipt, applications will be evaluated for completeness by CSR.
The NIH will not accept any application in response to this funding opportunity that is essentially the same as one currently pending initial review unless the applicant withdraws the pending application. The NIH will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of a substantial revision of an application already reviewed, but such application must include an Introduction addressing the previous critique.
Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within eight (8) weeks.

4. Intergovernmental Review

This initiative is not subject to intergovernmental review.

5. Funding Restrictions

All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm (see also Section VI.3. Reporting).
Pre-Award Costs are allowable. A grantee may, at its own risk and without NIH prior approval, incur obligations and expenditures to cover costs up to 90 days before the beginning date of the initial budget period of a new or competing continuation award if such costs: are necessary to conduct the project, and would be allowable under the grant, if awarded, without NIH prior approval. If specific expenditures would otherwise require prior approval, the grantee must obtain NIH approval before incurring the cost. NIH prior approval is required for any costs to be incurred more than 90 days before the beginning date of the initial budget period of a new or competing continuation award.
The incurrence of pre-award costs in anticipation of a competing or non-competing award imposes no obligation on NIH either to make the award or to increase the amount of the approved budget if an award is made for less than the amount anticipated and is inadequate to cover the pre-award costs incurred. NIH expects the grantee to be fully aware that pre-award costs result in borrowing against future support and that such borrowing must not impair the grantee's ability to accomplish the project objectives in the approved time frame or in any way adversely affect the conduct of the project. See NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part6.htm.

6. Other Submission Requirements

Because the applications will be co-funded by the NIH and the Tuberous Sclerosis Alliance all applicants should submit a brief letter to the NIH indicating that the application and the Summary Statements for such applications and the Progress Reports of funded grants can be shared with the Tuberous Sclerosis Alliance. Letters of authorization should be prepared by the principal investigator and co-signed by the official signing for the applicant organization. This letter may be submitted as a cover letter accompanying the application.
Specific Instructions for Modular Grant applications.
Applications requesting up to $250,000 per year in direct costs must be submitted in a modular budget format. The modular budget format simplifies the preparation of the budget in these applications by limiting the level of budgetary detail. Applicants request direct costs in $25,000 modules. Section C of the research grant application instructions for the PHS 398 at http://grants.nih.gov/grants/funding/phs398/phs398.html includes step-by-step guidance for preparing modular budgets. Applicants must use the currently approved version of the PHS 398. Additional information on modular budgets is available at http://grants.nih.gov/grants/funding/modular/modular.htm.
Specific Instructions for Applications Requesting $500,000 (direct costs) or More per Year.
Applicants requesting $500,000 or more in direct costs for any year must carry out the following steps:
1) Contact the IC program staff at least 6 weeks before submitting the application, i.e., as you are developing plans for the study;
2) Obtain agreement from the IC staff that the IC will accept your application for consideration for award; and,
3) Include a cover letter with the application that identifies the staff member and IC who agreed to accept assignment of the application.

This policy applies to all investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended or revised version of these grant application types. Additional information on this policy is available in the NIH Guide for Grants and Contracts, October 19, 2001 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-004.html.

Plan for Sharing Research Data

The precise content of the data-sharing plan will vary, depending on the data being collected and how the investigator is planning to share the data. Applicants who are planning to share data may wish to describe briefly the expected schedule for data sharing, the format of the final dataset, the documentation to be provided, whether or not any analytic tools also will be provided, whether or not a data-sharing agreement will be required and, if so, a brief description of such an agreement (including the criteria for deciding who can receive the data and whether or not any conditions will be placed on their use), and the mode of data sharing (e.g., under their own auspices by mailing a disk or posting data on their institutional or personal website, through a data archive or enclave). Investigators choosing to share under their own auspices may wish to enter into a data-sharing agreement. References to data sharing may also be appropriate in other sections of the application.

All applicants must include a plan for sharing research data in their application. The data sharing policy is available at http://grants.nih.gov/grants/policy/data_sharing. All investigators responding to this funding opportunity should include a description of how final research data will be shared, or explain why data sharing is not possible.

The reasonableness of the data sharing plan or the rationale for not sharing research data will be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or the priority score.

Sharing Research Resources

NIH policy requires that grant awardee recipients make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication (NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/index.htm and http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part7.htm#_Toc54600131). Investigators responding to this funding opportunity should include a plan for sharing research resources addressing how unique research resources will be shared or explain why sharing is not possible.

The adequacy of the resources sharing plan and any related data sharing plans will be considered by Program staff of the funding organization when making recommendations about funding applications. The effectiveness of the resource sharing will be evaluated as part of the administrative review of each non-competing Grant Progress Report (PHS 2590, http://grants.nih.gov/grants/funding/2590/2590.htm). See Section VI.3. Reporting.

The sharing of biomaterials, data, and software in a timely manner has been an essential element in the rapid progress that has been made in the genetic and molecular analysis of human diseases. All applicants who respond to this PAS must propose plans for sharing data and biomaterials generated through the grant. Applicants should explain how funds for the storage and distribution of data and biomaterials will be obtained, and may request such funds in the budget of the application. Biomaterials to be shared should include patient DNAs and cell lines, mouse or other animal models and other resources and reagents generated through the grant. When possible, data and biomaterials should be placed in databases or repositories that will permit their efficient distribution to investigators throughout the scientific community. Rapid sharing of data and biomaterials is strongly encouraged.

The Initial Review Group will evaluate the proposed sharing plan and comment on its adequacy in an administrative note in the Summary Statement. Reviewers will not factor the proposed data-sharing plan into the determination of scientific merit or priority score. The adequacy of the plan will be considered by NIH staff in determining whether the grant shall be awarded. The sharing plan as approved, after negotiation with the applicant when necessary, will be a condition of the award.

Section V. Application Review Information

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1. Criteria

Only the review criteria described below will be considered in the review process.

2. Review and Selection Process

Applications submitted for this funding opportunity will be assigned to the ICs on the basis of established PHS referral guidelines. Appropriate scientific review groups convened in accordance with the standard NIH peer review procedures (http://www.csr.nih.gov/refrev.htm) will evaluate applications for scientific and technical merit.

As part of the initial merit review, all applications will:

- Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score.
- Receive a written critique
- Receive a second level of review by the appropriate national advisory council or board and, when appropriate, by the Tuberous Sclerosis Alliance

The following will be considered in making funding decisions:

- Scientific merit of the proposed project as determined by peer review
- Availability of funds
- Relevance of program priorities

The goals of NIH-supported research are to advance our understanding of biological systems, to improve the control of disease, and to enhance health. In their written critiques, reviewers will be asked to comment on each of the following criteria in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed

and considered in assigning the overall score, weighting them as appropriate for each application. Note that an application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

1. Significance. Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge or clinical practice be advanced? What will be the effect of these studies on the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

2. Approach. Are the conceptual or clinical framework, design, methods, and analyses adequately developed, well integrated, well reasoned, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

3. Innovation. Is the project original and innovative? For example: Does the project challenge existing paradigms or clinical practice; address an innovative hypothesis or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches, methodologies, tools, or technologies for this area?

4. Investigators. Are the investigators appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers? Does the investigative team bring complementary and integrated expertise to the project (if applicable)?

5. Environment. Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed studies benefit from unique features of the scientific environment, or subject populations, or employ useful collaborative arrangements? Is there evidence of institutional support?

2.A. Additional Review Criteria:

In addition to the above criteria, the following items will continue to be considered in the determination of scientific merit and the priority score:

Protection of Human Subjects from Research Risk: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed (see the Research Plan, Section E on Human Subjects in the PHS Form 398).

Inclusion of Women, Minorities and Children in Research: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research will be assessed. Plans for the recruitment and retention of subjects will also be evaluated (see the Research Plan, Section E on Human Subjects in the PHS Form 398).

Care and Use of Vertebrate Animals in Research: If vertebrate animals are to be used in the project, the five items described under Section F of the PHS Form 398 research grant application instructions will be assessed.

2.B. Additional Review Considerations

Budget: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research. The priority score should not be affected by the evaluation of the budget.

2.C. Sharing Research Data

Data Sharing Plan: The reasonableness of the data sharing plan or the rationale for not sharing research data will be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or the priority score. The presence of a data sharing plan will be part of the terms and conditions of the award. The funding organization will be responsible for monitoring the data sharing policy.

2.D. Sharing Research Resources

NIH policy requires that grant awardee recipients make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication (See the NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps/part_ii_5.htm#availofrr and http://ott.od.nih.gov/newpages/rtguide_final.html). Investigators responding to this funding opportunity should include a sharing research resources plan addressing how unique research resources will be shared or explain why sharing is not possible.

The adequacy of the resources sharing plan will be considered by Program staff of the funding organization when making recommendations about funding applications. Program staff may negotiate modifications of the data and resource sharing plans with the awardee before recommending funding of an application. The final version of the data and resource sharing plans negotiated by both will become a condition of the award of the grant. The effectiveness of the resource sharing will be evaluated as part of the administrative review of each non-competing Grant Progress Report (PHS 2590). See Section VI.3. Reporting.

3. Anticipated Announcement and Award Dates

Not Applicable

Section VI. Award Administration Information

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1. Award Notices

After the peer review of the application is completed, the Principal Investigator will also receive a written critique called a Summary Statement.

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant. For details, applicants may refer to the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part4.htm).

A formal notification in the form of a Notice of Grant Award (NGA) will be provided to the applicant organization. The NGA signed by the grants management officer is the authorizing document.

The Notice of Grant Award will be sent by e-mail to the designated institutional official listed on the face page of the application or may be retrieved by the institution through its NIH eRA Commons account. If a grantee is not e-mail enabled, a hard copy of the NGA will be mailed to the institutional official.

Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NGA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs. See Also Section IV.5. Funding Restrictions.

2. Administrative and National Policy Requirements

The terms and conditions of the award may include specific requirements for data and/or resource sharing including depositing cell lines, DNA samples, biomaterials or other mouse and animal models into National repositories.
Additional Award Criteria may include the adequacy of the sharing plan for data and resources generated under the award.
All NIH grant and cooperative agreement awards include the NIH Grants Policy Statement as part of the notice of grant award. For these terms of award, see the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part4.htm) and Part II Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part9.htm).

3. Reporting

Awardees will be required to submit the PHS Non-Competing Grant Progress Report, Form 2590 annually (http://grants.nih.gov/grants/funding/2590/2590.htm) and financial statements as required in the NIH Grants Policy Statement.

Section VII. Agency Contacts

We encourage your inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

1. Scientific/Research Contacts:

Robert Finkelstein, Ph.D.
Associate Director for Extramural Research
National Institute of Neurological Disorders & Stroke
6001 Executive Blvd., Room 3307
Bethesda, MD 20892-9531
Phone: (301) 496-9248
Email: finkelsr@ninds.nih.gov
Elizabeth L. Wilder, Ph.D.
Program Director
Division of Kidney, Urologic, and Hematologic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
6707 Democracy Blvd., Rm. 623
Bethesda, MD 20892-5458
Phone: (301) 594-1409
Email: betsywilder@nih.gov
Mary Ellen Perry, Ph. D.
Program Director
Division of Cancer Biology
National Cancer Institute
EPN 5034
Bethesda, MD 20892-7396
Phone: (301) 496-7028
Email: mp372j@nih.gov
Alan N Moshell, MD
Skin Disease Branch Chief
National Institute of Arthritis and Musculoskeletal and Skin Diseases
One Democracy Plaza
6701 Democracy Blvd
Bethesda, MD 20892-4872
Phone: (301) 594-5017
Email: alan_n_moshell@nih.gov
Ann Wagner, Ph.D.
Chief, Neurodevelopmental Disorders Branch
Division of Pediatric Translational Research and Treatment Development
National Institute of Mental Health
6001 Executive Blvd.
Room 6229, MSC 9623
Bethesda, MD 20892-9623
Phone: (301) 443-3633
Email: awagner@mail.nih.gov

2. Peer Review Contacts:

Not Applicable

3. Financial or Grants Management Contacts:

Ms. Kathleen Howe
Grants Management Branch

National Institute of Neurological Disorders and Stroke
6001 Executive Boulevard, Room 3266
Bethesda, MD 20892
Telephone: (301) 496-9231
FAX: (301) 402-0219
Email: howek@ninds.nih.gov

Section VIII. Other Information

Required Federal Citations

Use of Animals in Research:
Recipients of PHS support for activated involving live, vertebrate animals must comply with PHS Policy on Humane Care and Use of Laboratory Animals (http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf) as mandated by the Health Research Extension Act of 1985 (http://grants.nih.gov/grants/olaw/references/hrea1985.htm), and the USDA Animal Welfare Regulations (http://www.nal.usda.gov/awic/legislat/usdaleg1.htm) as applicable.

Human Subjects Protection:
Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm).

Data and Safety Monitoring Plan:
Data and safety monitoring is required for all types of clinical trials, including physiologic toxicity and dose-finding studies (phase I); efficacy studies (Phase II); efficacy, effectiveness and comparative trials (Phase III). Monitoring should be commensurate with risk. The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risks to the participants (NIH Policy for Data and Safety Monitoring, NIH Guide for Grants and Contracts, http://grants.nih.gov/grants/guide/notice-files/not98-084.html).

Sharing Research Data:
Investigators submitting an NIH application seeking $500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why this is not possible (http://grants.nih.gov/grants/policy/data_sharing).
Investigators should seek guidance from their institutions, on issues related to institutional policies and local IRB rules, as well as local, State and Federal laws and regulations, including the Privacy Rule. Reviewers will consider the data sharing plan but will not factor the plan into the determination of the scientific merit or the priority score.

Sharing of Model Organisms:
NIH is committed to support efforts that encourage sharing of important research resources including the sharing of model organisms for biomedical research (see http://grants.nih.gov/grants/policy/model_organism/index.htm). At the same time the NIH recognizes the rights of grantees and contractors to elect and retain title to subject inventions developed with Federal funding pursuant to the Bayh Dole Act (see the NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/index.htm). All investigators submitting an NIH application or contract proposal, beginning with the October 1, 2004 receipt date, are expected to include in the application/proposal a description of a specific plan for sharing and distributing unique model organism research resources generated using NIH funding or state why such sharing is restricted or not possible. This will permit other researchers to benefit from the resources developed with public funding. The inclusion of a model organism sharing plan is not subject to a cost threshold in any year and is expected to be included in all applications where the development of model organisms is anticipated.

Inclusion of Women And Minorities in Clinical Research:
It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43). All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html); a complete copy of the updated Guidelines is available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

Inclusion of Children as Participants in Clinical Research:
The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.
All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects (http://grants.nih.gov/grants/funding/children/children.htm).

Required Education on the Protection of Human Subject Participants:
NIH policy requires education on the protection of human subject participants for all investigators submitting NIH applications for research involving human subjects and individuals designated as key personnel. The policy is available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

Human Embryonic Stem Cells (hESC):
Criteria for federal funding of research on hESCs can be found at http://stemcells.nih.gov/index.asp and at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (http://escr.nih.gov/). It is the responsibility of the applicant to

provide in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s)to be used in the proposed research. Applications that do not provide this information will be returned without review.

Public Access to Research Data through the Freedom of Information Act:

The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm. Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

Standards for Privacy of Individually Identifiable Health Information:

The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information", the "Privacy Rule", on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (http://www.hhs.gov/ocr/) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html.

URLs in NIH Grant Applications or Appendices:

All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

Healthy People 2010:

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This PA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople.

Authority and Regulations: This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov/ and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Loan Repayment Programs:

NIH encourages applications for educational loan repayment from qualified health professionals who have made a commitment to pursue a research career involving clinical, pediatric, contraception, infertility, and health disparities related areas. The LRP is an important component of NIH's efforts to recruit and retain the next generation of researchers by providing the means for developing a research career unfettered by the burden of student loan debt. Note that an NIH grant is not required for eligibility and concurrent career award and LRP applications are encouraged. The periods of career award and LRP award may overlap providing the LRP recipient with the required commitment of time and effort, as LRP awardees must commit at least 50% of their time (at least 20 hours per week based on a 40 hour week) for two years to the research. For further information, please see: http://www.lrp.nih.gov/.

Weekly TOC for this Announcement
NIH Funding Opportunities and Notices

Department of Health and Human Services

National Institutes of Health (NIH)
9000 Rockville Pike
Bethesda, Maryland 20892